CLAIMS:

1. A bidentate motif capable of binding a cytoplasmic protein and activating cellular activities in a cell, said bidentate motif comprising a tyrosine and a serine/threonine residue which are capable of interaction with cytoplasmic proteins, and wherein the residue and cytoplasmic protein can interact to activate cellular activity in the cell.

2. A bidentate motif according to claim 1 wherein the tyrosine and serine/threonine residue comprises a binary switch for independent regulation of cellular activity.

3. A bidentate motif capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following amino acid sequence alignment:

$$N\text{-}X\text{-}X\text{-}\underline{Y}\text{-}(X)_{1\text{-}13}\text{-}[R/K/H/Q]\text{-}[X/\Psi]_{2\text{-}3}\text{-}\underline{S/T}\text{-}X\text{-}P$$

wherein X is any residue, Y is tyrosine, S/T is serine or threonine and Ψ is a hydrophibic residue or an equivalent thereof.

4. A bidentate motif capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following amino acid sequence alignment:

$$\underline{Y}\text{-}(X)_{1\text{-}16}\text{-}[R/K/H/Q]\text{-}[X/\Psi]_{2\text{-}3}\text{-}\underline{S/T}\text{-}X\text{-}P$$

wherein X is any residue, Y is tyrosine, S/T is serine or threonine and Ψ is a hydrophibic residue or an equivalent thereof.

5. A bidentate motif capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following sequence alignment:

$$N\text{-}X\text{-}X\text{-}\underline{Y}\text{-}[X]_{1\text{-}30}\text{-}[R/K/Q/H]\text{-}[X]_{1\text{-}4}\text{-}[\underline{S/T}]\text{-}X\text{-}p$$

wherein X is any residue, $\underline{Y}$ is phosphotyrosine, $\underline{S/T}$ is phosphoserine/phosphothreonine.

6. A bidentate motif of a receptor molecule capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following amino acid sequence alignment:

$$N\text{-}X\text{-}X\text{-}\underline{Y}\text{-}(X)_{1\text{-}13}\text{-}[R/K/H/Q]\text{-}[X/\Psi]_{2\text{-}3}\text{-}\underline{S/T}\text{-}X\text{-}P$$

wherein X is any residue, Y is tyrosine, S/T is serine or threonine and Ψ is a hydrophibic residue or an equivalent thereof.

7. A bidentate motif of a receptor molecule capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following amino acid sequence alignment:

$$\underline{Y}\text{-}(X)_{1\text{-}16}\text{-}[R/K/H/Q]\text{-}[X/\Psi]_{2\text{-}3}\text{-}\underline{S/T}\text{-}X\text{-}P$$

wherein X is any residue, Y is tyrosine, S/T is serine or threonine and Ψ is a hydrophibic residue or an equivalent thereof.

8. A bidentate motif of a receptor capable of binding to a cytoplasmic protein comprising a tyrosine and a serine/threonine residue, said motif consisting of the following sequence alignment:

$$N\text{-}X\text{-}X\text{-}\underline{Y}\text{-}[X]_{1\text{-}30}\text{-}[R/K/Q/H]\text{-}[X]_{1\text{-}4}\text{-}[\underline{S/T}]\text{-}X\text{-}p$$

wherein X is any residue, $\underline{Y}$ is phosphotyrosine, $\underline{S/T}$ is phosphoserine/phosphothreonine.

9. A bidentate motif according to any one of claims 1 to 8 from a receptor selected from the group including

(1) GM-CSF/IL-3/IL-5 receptor
(2) IL6 human interleukin-6 receptor beta chain precursor (IL-6R-beta)
(3) LEPR human leptin receptor precursor (LEP-R) (OB RECEPTOR) (OB-R).
(4) TNR2 human tumor necrosis factor receptor 2 precursor (tumor necrosis factor
(5) VGR1 human vascular endothelial growth factor receptor 1 precursor
(6) TRK3 human receptor protein-tyrosine kinase TKT precursor (EC 2.7.1.112)
(7) Q01974 protein-tyrosine kinase transmembrane receptor ROR2 precursor

(8) FGR1 human basic fibroblast growth factor receptor 1 precursor (BFGF-R)

(9) Q15426 protein-tyrosine phosphatase, receptor-type, H precursor (EC 3.1.3.48)

(10) PTPM human protein-tyrosine phosphatase mu precursor (EC 3.1.3.48) (R-PTP-MU).

(11) PDGS human alpha platelet-derived growth factor receptor precursor (EC 2.7.1.112)

(12) FGR4 human fibroblast growth factor receptor 4 precursor (FGFR-4) (EC 2.7.1.112)

(13) FGR2 human fibroblast growth factor receptor 2 precursor (FGFR-2) (EC 2.7.1.112)

(14) Q13635 patched protein homolog (PTC)

(15) MANR human macrophage mannose receptor precursor.

(16) LRP2 human low-density lipoprotein receptor-related protein 2 precursor (megalin)

(17) IDD human integral membrane protein dgcr2/idd precursor (KIAA0163)

(18) AMFR human autocrine motility factor receptor precursor (AMF receptor) (gp78)

(19) ACH5 human neuronal acetylcholine receptor protein, alpha-5 chain precursor.

(20) KKIT human: stem cell growth factor receptor (proto-oncogene tyrosine-protein kinase kit) (C-KIT) (CD117 antigen)

(21) TPOR human: thrombopoietin receptor precusor (TPO-R) (myeloproliferative leukemia protein (C-MPL). TPOR or MPL.

(22) TPOR mouse: thrombopoietin receptor precursor (TPO-R) (myeloproliferative leukemia protein) (C-MPL). TPOR or MPL.

(23) Acetylcholine R

(24) Acetylcholine R alpha-5

(25) C-C chemokine receptor 6

(26) Middle T antigen

(27) integrin alpha 1

(28) FGFR2 (KGF R)
(29) FGFR1 (flg)
(30) FGFR5
(30) Erb4
(31) Vaccinia virus protein A36R
(32) Macrophage mannose R (MRC1)
(33) LDLR
(34) VLDL (rat)
(35) LRP1 low density lipoprotein receptor-related protein 1
(36) integrin beta 1
(37) interin beta 7
(38) integrin beta 3
(39) integrin beta 5
(40) integrin beta 6
(41) G-CSFR1 (second)
(42) g-csf-r
(43) IL-6B (gp130)
(44) LeptinR
(45) ProlactinR
(46) insulinR
(47) irs-1
(48) IGFI R
(49) flt3 R
(50) VEGFR2 (FLK1)
(51) PDGF R-alpha
(52) IL-9R
(53) Beta R
(54) Neuronal acetylcholine receptor protein, alpha-3 chain
(55) protein tyrosine phosphatase receptor N
(56) glycogen synthase kinase 3 alpha
(57) p21-activated kinase 3
(58) 3-phosphoinositide dependent protein kinaes-1 (PDK1)
(59) integrin alpha 1 (laminin/collagen receptor)

or a functional equivalent or analogue thereof.

10. A bidentate motif according to any one of claims 1 to 9 having a sequence selected from the group including:

NGPYLG.....PP..HSRSLP
NVHYRT.....P...KTHTMP
**RYFTQKEE.....TESGSGP
NKKYELQDRDVCE....P.RYRSVSEP
NPTYSVM.....RSHSYP
NIFYLIR...KSGSFPMPELKLSISFP
NEEYLDLSQ.....PLEQYSPSYP
NQEYLDLSM.....PLDQYSPSFP
NATYKVD.....VIQRTRSKP
NPEY.....HSASSGP
NPDY.....WNHSLP
NPSYSSNPFVNYN....KTSICSKSNP
NTLY.....FNSQSSP
NPVYQKTTEDEVHI...CHNQDGYSYP
NPVYLKTTEEDLSIDIG..RH.SASVG
NPTYKMYEGGEPDDVGGLLDADFALDPDKPTNFTNPVY
NPIY.....KSAVTTVV
NPLY.....KSAITTTV
NPLY.....KEATSTFT
NPLY.....RKPISTHT
NPLY.....RGSTSTFK
PGHYL.....RCDSTQP
VQTYVLQ.....GDPRAVSTQP
QVLYGQLL.....GSPTSP
HSGYRHQVPSVQVF.....SRSESTQP
WKMYEVYDA.....KS.KSVSLP
KIPYFHA.....GGS.KCSTWP
ELDYCLKGLKL.....P.S.RTWSPP
SGDYMPM.....SPKSVSAP
SFYYSEENKLPEPEELDLEPENMESVP(LDPSASSSSLP)
EEIYIIM.....QSCWAFDSRKRPSFP
ISQYLQN.....S.KRKSRP
GTAY.....GLSRSQP
***YLPQEDWAP.....TSLTRP
LVAYIAFKRWNSCKQN...KQGANSRPVNQTPPPEGEKLHSDSGIS

11. A bidentate motif according to any one of claims 1 to 10 wherein the motif is derived from a cytokine receptor.

12. A bidentate motif according to any one of claims 1 to 11 wherein the cytokine receptor is the GM-CSF/IL-3/IL-5 receptor.

13. A bidentate motif according to any one of claims 1 to 12 wherein the motif is derived from the common beta chain (βc).

14. A bidentate motif according to any one of claims 1 to 13 wherein the Tyr is equivalent to Tyr577 of the common beta chain (βc).

15. A bidetate motif according to any one of claims 1 to 14 wherein the Ser is equivalent to Ser 585 of the common beta chain (βc).

16. A bidentate motif according to any one of claims 1 to 15 wherein the tyrosine or serine/threonine independently phosphorylate in response to cytokine concentration

17. A bidentate motif according to any one of claims 1 to 16 wherein phosphorylation of the serine independently of the tyrosine regulates cell survival.

18. A bidentate motif according to claim 16 or 17 wherein the cytokine concentration is less than 10pM, preferably 3pM, more preferably 1pM.

19. A bidentate motif according to any one of claims 1 to 16 wherein phosphorylation of the tyrosine independently of the serine regulates cell survival and proliferation.

20. A bidentate motif according to claim 18 or 19 wherein the cytokine concentration is greater than 10pM.

21. A bidentate motif according to any one of claims 1 to 20 which binds to at least one cytoplasmic protein selected from the group including 14-3-3 protein, Shc, SHIP-2, WW-domain of the prolyl isomerase, Pin1 and the ubiquitin ligase, NEDD4.

22. A bidentate motif according to claim 21 wherein the cytoplasmic protein is 14-3-3, Shc or SHIP-2.

23. A bidentate motif according to any one of claims 1 to 22 wherein the Tyr binds to the Shc.

24. A bidentate motif according to any one of claims 1 to 23 wherein the Ser binds to 14-3-3.

25. A bidentate motif according to any one of claims 1 to 20 having a modification at a residue equivalent to the Tyr and/Ser.

26. A bidentate motif according to claim 25 wherein the residue equivalent to Tyr is substituted with Phe.

27. A bidentate motif according to claim 25 or 26 wherein the Ser residue is substituted with Gly.

28. A method of modulating cellular activity in a cell, said method comprising: modifying phosphorylation of a Tyr and/or Ser residue of a bidentate motif according to any one of claims 1 to 27.

29. A method according to claim 28 wherein the Tyr is equivalent to Tyr577 and Ser is equivalent to 585 of the common beta chain (βc) in a cell.

30. A method according to claim 29 wherein the common beta chain (βc) is from the GM-CSF/IL-3/IL-5 receptor.

31. A method according to any one of claims 28 to 30 wherein the cellular activity is modulated by increasing or decreasing phosphorylation of the Tyr and/or Ser residue of the bidentate motif.

32. A method according to claim 31 wherein the phosphorylation is increased by subjecting the cell to a phosphorylating agent.

33. A method according to claim 32 wherein the phosphorylating agent is a kinase.

34. A method according to claim 31 wherein the phosphorylation is decreased by mutating the Tyr and/or Ser.

35. A method according to claim 34 wherein the Tyr is substituted for Phe and/or the Ser is substituted for Gly.

36. A method according to claim 31 wherein the phosphorylation is decreased by subjecting the cell to an antagonist which inhibits phosphorylation of the Tyr and/or Ser.

37. A method according to claim 31 wherein the phosphorylation is decreased by subjecting the cell to a kinase inhibitor to inhibit phosphorylation of the Tyr and/or Ser.

38. A method according to claim 31 wherein the phosphorylation is modulated by exposing the cell to a cytokine.

39. A method according to claim 38 wherein the cytokine is GM-CSF.

40. A method according to any one of claims 28 to 38 for inhibiting cellular activity, said method comprising decreasing or inhibiting phosphorylation of the Tyr and/or Ser of the bidentate motif.

41. A method according to claim 40 wherein the cellular activity is cell survival, said method comprising inhibiting phosphorylation of the serine.

42. A method according to claim 41 wherein the serine is equivalent to Ser585 of the common beta chain (βc).

43. A method according to any one of claims 40 to 42 for inhibiting cellular activity, said method further comprising inhibiting binding of a cytoplasmic protein to the bidentate motif.

44. A method according to claim 43 wherein the cytoplasmic protein is selected from the group including 14-3-3 protein, Shc, SHIP-2, WW-domain of the prolyl isomerase, Pin1 and the ubiquitin ligase, NEDD4.

45. A method according to claim 43 or 44 wherein the cytoplasmic protein is 14-3-3 or Shc.

46. A method according to any one of claims 28 to 38 for activating cellular activity, said method comprising inducing phosphorylation of the Tyr and/or Ser of the bidentate motif.

47. A method according to claim 46 wherein the cellular activity is cell survival, said method comprising increasing phophorylation of the serine.

48. A method according to claim 47 wherein the cell is exposed to GM-CSF at a concentration of up to 10pM, preferably 3pM, more preferably 1pM.

49. A method according to claim 46 wherein the cellular activity is cell proliferation, said method comprising increasing phosphorylation of the tyrosine.

50. A method according to claim 49 wherein the cell is exposed to at least 10pM. GM-CSF.

51. A method according to any one of claims 28 to 50 further including modifying an interaction between the cytoplasmic protein 14-3-3, Shc and Ty179 on the 14-3-3.

52. A method according to claim 51 including inhibiting an interaction between the cytoplasmic protein 14-3-3, Shc and Tyr 179 on the 14-3-3.

53. A method according to any one of claims 28 to 52 wherein the cell is a haematopoietic cell.

54. A method of treating a cytokine mediated condition, said method comprising:

regulating activation of phosphorylation the tyrosine and/or serine of a bidentate motif according to any one of claims 1 to 27.

55. A method according to claim 54 wherein the Tyr is equivalent to Tyr 577 and Ser is equivalent to Ser 585 of the common beta chain (βc).

56. A method according to claim 54 or 55 wherein the common beta chain (βc) is of the GM-CSF/IL-3/IL-5 receptor.

57. A method according to any one of claims 54 to 56 wherein the cytokine mediated condition is treated by increasing or decreasing activation of phosphorylation of the tyrosine and/or serine of the bidentate motif.

58. A method according to claim 57 wherein the phosphorylation is increased by subjecting the cell to a phosphorylating agent.

59. A method according to claim 58 wherein the phosphorylating agent is a kinase.

60. A method according to claim 57 wherein the phosphorylation is decreased by mutating the Tyr and/or Ser.

61. A method according to claim 60 wherein the Tyr is substituted for Phe and/or the Ser is substituted for Gly.

62. A method according to claim 57 wherein the phosphorylation is decreased by subjecting the cell to an antagonist which inhibits phosphorylation of the Tyr and/or Ser.

63. A method according to claim 57 wherein the phosphorylation is decreased by subjecting the cell to a kinase inhibitor to inhibit phosphorylation of the Tyr and/or Ser.

64. A method according to claim 54 wherein the phosphorylation is regulated by exposing the cell to a cytokine.

65. A method according to claim 64 wherein the cytokine is GM-CSF.

66. A method according to any one of claims 54 to 65 wherein the cytokine mediated condition is a GM-CSF mediated condition.

67. A method according to claim 54 wherein the cytokine mediated condition involves cell survival.

68. A method according to claim 67 for improving cell survival, said method including subjecting the cell to GM-CSF.

69. A method according to claim 68 wherein the GM-CSF is at a concentration of up to 10pM, preferably 3pM, more preferably 1pM.

70. A method according to claim 54 wherein the cell modulated condition involves cell proliferation.

71. A method according to claim 70 for improving cell proliferation, said method comprising subjecting the cell to GM-CSF.

72. A method according to claim 71 comprising subjecting the cell to greater than 10pM GM-CSF.

73. A method according to claim 54 wherein the cytokine indicated condition is carrier.

74. A method according to claim 73 comprising inhibiting phosphorylation of the tyrosine and serine.

75 .A method according to claim 54 wherein the cytokine mediated condition is selected from the group including myeloid cell activation, asthma and rheumatoid arthritis.

76. A method for diagnosing a proliferative condition involving cell proliferation or cell survival, said method including:

detecting a level of phosphorylation of Tyr and/or Ser in a bidentate motif according to any one of claims 1 to 27 in a cell; and

comparing against a cell of a normal level of phosphorylation.

77. A method according to claim 76 wherein the Tyr is equivalent to Tyr577 and Ser is equivalent to Ser585 of the common beta chain (βc).

78. A method according to claim 76 or 77 wherein the common beta chain (βc) is from the GM-CSF/IL-3/IL-5 receptor.

79. A method according to any one of claims 76 to 78 wherein the cell is a haematopoietic cell.